Remarks

Reconsideration of this Application is respectfully requested.

Claims 84-122 and 127-131 are pending in the application, with claims 84 and 127 being the independent claims. Claims 123-126 were previously canceled without prejudice. Applicants reserve the right to pursue the canceled subject matter in related applications. Claims 98, 100-102, and 104-106 have been withdrawn from consideration by the Examiner as reading solely on non-elected species, but remain pending. Claims 34, 86, 87, 89, 90, 91, 93-97, 107, 110, 113-120, 128, 129, and 131 are sought to be amended. Support for the amendments can be found, *inter alia*, throughout the specification and claims as originally filed. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendments and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Applicants also respectfully remind the Examiner that, in view of the amendments and remarks presented herein, that the present claims "would not have been properly finally rejected on the grounds and art of record in the next Office Action." M.P.E.P. § 706.07(b). Therefore, Applicants respectfully submit that the issuance of a final Office Action after the filing of the present Amendment and Reply and the Request for Continued Examination, filed concurrently herewith, would be improper.

Rejections under 35 U.S.C. § 103

The rejection of claims 84, 88-97, 99, 103, 107-122, and 127-131 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Rowlands *et al.*, WO 93/01296 (hereinafter "Rowlands"), Zauderer, WO 00/28016 (hereinafter "Zauderer"), and Waterhouse *et al.*, *Nuc. Acids Res.* 21: 2265-66 (1993) (hereinafter "Waterhouse") was maintained. *See* Office Action dated November 2, 2005 ("present Office Action"), at pages 2-3. Applicants respectfully traverse this rejection.

The Rejection of Claims 84, 88-97, 99, 103, 107-122, and 127-131 as Presented in Applicants' Reply Filed July 21, 2005, is Traversed.

Applicants note that, although they seek to amend the claims in the captioned application, the amendments made herein are solely to facilitate prosecution, and are not in acquiescence to the Examiner's rejections. Applicants reserve the right to pursue the subject matter of the claims in the form presented in the Reply of July 21, 2005 (which is herein incorporated by reference), in one or more continuing applications. Applicants therefore provide the following remarks as to why the rejection under 35 U.S.C. § 103, as it applies to the claims as presented in the Reply of July 21, 2005, is improper.

In maintaining the rejection of claims 84, 88-97, 99, 103, 107-122, and 127-131 under 35 U.S.C. § 103 in the present Office Action, the Examiner has essentially repeated the same arguments as set forth in the previous Office Action, dated April 21, 2005. In response, Applicants reiterate and maintain their arguments as set forth in Reply filed on July 21, 2005, incorporated herein by reference in its entirety. In the present Office Action, the Examiner also addressed the Applicants arguments as presented in the Reply filed on July 21, 2005, to which Applicants provide the following reply and remarks in the same order as set forth in the present Office Action:

Item [1]

The Examiner disagrees with Applicants that the cited references do not teach or suggest the introduction of two expression libraries into eukaryotic host cells. *See* present Office Action at pages 10 and 12. As support for his disagreement, the Examiner asserts that: "Applicants have already acknowledged that the combined references teach the use of two libraries," citing to Applicants' previous Reply dated July 21, 2005. Present Office Action at page 12. However, Applicants believe that the statements in the previous Reply have been mischaracterized in the present Office Action.

In the previous Reply, Applicants stated that Waterhouse (not the combined references) discloses the introduction of bacteriophage vectors encoding immunoglobulin heavy and light chain variable region fragments that can undergo Cre-*lox* regulated site-specific recombination into bacterial, i.e., ***prokaryotic***, host cells, and suggests that this ***prokaryotic*** system can be used to generate large combinatorial libraries by providing repertoires of heavy and light chain fragments. From this, the Examiner seems to have mistakenly drawn the conclusion that Applicants have acknowledged that the references teach or suggest the introduction of two expression libraries into eukaryotic host cells, a conclusion with which the Applicants respectfully but wholeheartedly disagree. Applicants respectfully maintain and emphasize that the cited references **do not** teach or suggest the introduction of two expression libraries into eukaryotic host cells for selecting polynucleotides which encode an antigen-specific human immunoglobulin molecule, as in the present invention, nor have they acknowledged at any time that the cited references, either combined or individually, provide such a teaching.

Item [2]

In the present Office Action, the Examiner maintains that one of ordinary skill in the art would have been motivated to combine Rowlands, Zauderer, and Waterhouse. *See* present Office Action at pages 10 and 13. In particular, the Examiner asserts that:

> . . one of ordinary skill in the art would have been motivated to make libraries as taught by Zauderer et al. using the heavy/light chain antibodies as disclosed by Rowlands et al. because Zauderer et al. explicitly state that the [sic] their "tri-molecular" approach represents an easy and efficient means for generating a library in vaccinia virus vectors in mammalian cells, which is a preferred embodiment for Rowlands et al.

Id. at 13. The Examiner further asserts that "Waterhouse et al. teach that 'associated' light and heavy chains are a 'preferred' embodiment for screening and/or affinity maturation because they can be 'simultaneously co-selected'. . .which would encompass the 'associated' heavy/light chains described by Rowlands et al." *Id.* at 13 (internal citations omitted). Applicants respectfully disagree with these assertions.

Although both Rowlands and Zauderer disclose the use of vaccinia virus expression vectors in eukaryotic cells, Applicants maintain that there is no motivation or suggestion for one of ordinary skill in the art to combine these references to introduce ***two expression libraries*** encoding immunoglobulin subunit polypeptides into ***eukaryotic*** cells for selecting polynucleotides which encode an antigen-specific human immunoglobulin molecule because Rowlands discloses the expression of a previously selected antibody (*i.e.*, not separate, randomly introduced libraries of immunoglobulin light and heavy chains), and Zauderer discloses the introduction of a single expression library into eukaryotic host cells (*i.e.*, not two separate expression libraries of immunoglobulin light and heavy chains).

Furthermore, the "associated heavy and light chains" in Rowlands are not the same as the "associated heavy and light chains" that can be "simultaneously co-selected" in Waterhouse, as suggested by the Examiner, *see* present Office Action at page 13, and both types of "associated heavy and light chains" as disclosed in Rowlands and Waterhouse are different from the present invention. As set forth in Applicants' previous Replies, as well as in the Declaration of Dr. Walter J. Storkus ("Storkus Declaration"), which was filed as Exhibit A with the Reply filed on July 21, 2005 (all of which are incorporated herein by reference), Rowlands demonstrated the expression of a single antibody that had already been selected for heavy and light chains that paired correctly and efficiently (*i.e.*, the CDR-grafted Campath-1H antibody). *See e.g.,* Storkus Declaration at page 5. Waterhouse, on the other hand, describes simultaneous co-selection of antibody heavy and light chain fragments from prokaryotic host cells that have been recombined by site-specific recombination and which is facilitated by the incorporation of the immunoglobulin heavy and light chain variable regions as part of the same vector:

> In principle, larger repertoires could be made by combinatorial infection, for example by transforming *E. coli* with a repertoire of heavy chains (encoded on plasmids) then infecting with a repertoire of light chains (encoded on phage). . . However, the heavy and light chain genes *would not be packaged together within the same phage particle* and so *could not be simultaneously co-selected.* Here we describe a model system, involving the *lox*-Cre site-specific recombination system of bacteriophage P1, *to lock together the heavy and light chain genes from two different replicons within an infected bacterium.*

Waterhouse at page 2265, column 1 (emphasis added). This type of co-selection of heavy and light chain fragments expressed from a common vector does not teach or suggest that heavy and light chains would associate to form an antigen-specific

immunoglobulin as in the present invention, wherein separate, random heavy and light chain libraries in *separate vectors* are introduced into eukaryotic cells. The teaching or suggestion to combine does not come from Rowlands, because Rowlands discloses expression of a single, previously selected antibody. The teaching or suggestion does not come from Zauderer, because Zauderer discloses introduction of one eukaryotic expression library into host cells, not introduction of two separate expression libraries. With respect to a motivation to combine these references, as discussed in the Storkus Declaration, there are differences in the way that proteins assemble in eukaryotic cytoplasm as opposed to prokaryotic periplasm. *See* Storkus Declaration at page 3-4. Dr. Storkus further indicated that random pairs of immunoglobulin heavy and light chains derived from separate eukaryotic expression libraries would be expected to be poorly matched and, therefore, would be expected not to associate properly in the eukaryotic cytoplasm. *Id.* at 4.

The Examiner impermissibly is using the Applicants' own claimed invention as a blueprint to select only those features from each reference that the Examiner believes will support a *prima facie* case of obviousness. The Examiner identifies Rowlands as differing from the claimed invention in that "[Rowlands et al.] do not specifically teach the use of a 'library' of first/second polynucleotides." Present Office Action at page 5. The Examiner further states that, "[h]owever, Zauderer et al. and Waterhouse et al. teach the following limitations that are deficient in Rowlands et al." *Id.* In particular, the Examiner asserts that Zauderer discloses "the use of a 'library of polynucleotides in a vaccinia virus vector using the 'tri-molecular recombination' approach for screening purposes," and that Waterhouse discloses "that a 'library' can be usefully employed to

screen for antibodies with high affinity to various antigens including the use of heavy/light chains that are 'packaged together' i.e., two libraries." *Id.* at pages 5-6 (emphasis in original). Although the Examiner points to the cited references as supplying all of the elements of the present invention, a point with which Applicants respectfully disagree, this is not sufficient for establishing a *prima facie* case of obviousness under 35 U.S.C. § 103. "[R]ejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention. Such an approach would be 'an illogical and inappropriate process by which to determine patentability.'" *In re Rouffet*, 149 F.3d 1350, 1375 47 U.S.P.Q.2d 1453 (Fed. Cir. 1998) (quoting *Sensonics, Inc. v. Aerosonic Corp.* 81 F.3d 1566, 1570, 38 U.S.P.Q.2d 1551, 1554 (Fed. Cir. 1996). *See also, In re Fine*, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988) ("One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.").

In *Fine*, the applicants' claims to a system for detecting and measuring minute quantities of nitrogen-containing compounds were rejected as obvious over the combination of the Eads and Warnick references. *Fine*, 837 F.2d at 1073. The Federal Circuit found that "[t]here is no suggestion in Eads, which focuses on the unique difficulties inherent in the measurement of sulfur, to use that arrangement to detect nitrogen compounds." *Id.* at 1074. The Federal Circuit also determined that the teachings of Warnick "are inconsistent with the claimed invention, to some extent," because:

> [Warnick] contemplates measuring the total amount of nitric oxide in a continuously flowing gaseous mixture of unseparated nitrogen constituents. By contrast, in Fine each nitrogen compound constituent of the gaseous sample is retained in the chromatograph for an individual time period so that each exits in discrete, time-separated pulses. . . . The claimed system, therefore, diverges from Warnick and teaches advantages not appreciated or contemplated by it.

Id. at 1074-75. The Federal Circuit concluded that, "[b]ecause neither Warnick nor Eads, alone or in combination, suggests the claimed invention, the Board erred in affirming the Examiner's conclusion that it would have been obvious to substitute the Warnick nitric oxide detector for the Eads sulfur dioxide detector in the Eads system." *Id.* at 1075.

In the present case, Waterhouse discloses methods of making combinatorial antibody repertoires for selection using phage display. As with respect to the Warnick reference in *Fine*, the present invention diverges from Waterhouse and teaches advantages not appreciated or contemplated by it. Namely, the methods of the present invention are performed using eukaryotic cells and allow selection of an immunoglobulin of interest by introducing two separate, expression libraries of heavy and light chains into eukaryotic host cells. The advantages of performing immunoglobulin screening and selection in eukaryotic cells are discussed in detail in the Declaration of Dr. Maurice Zauderer ("Zauderer Declaration"), filed as Exhibit B with Applicants' Reply filed July 21, 2005, and include, for example, the ability to screen for antibodies that are specific for membrane-associated proteins, the ability to screen for functionality as well as binding activity, and the eukaryotic post-translational modification and assembly that does not occur when antibody fragments are screened and selected by phage display, and which can affect binding and specificity of phage-selected antibodies when the fragments

are removed from the phage fusion protein context. *See* Zauderer Declaration at pages 4, 7, and 8.

Furthermore, the law requires considering each of the cited references *as a whole* in establishing a *prima facie* case of obviousness. "'It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.'" *In re Hedges*, 783 F.2d 1038, 1041, 228 U.S.P.Q. 685 (Fed. Cir. 1986) (quoting *In re Wesslau*, 353 F.2d 238, 241 147, U.S.P.Q. 391, 393 (CCPA 1965)) (underline in original).

In the present case, the Examiner relies on Waterhouse "to show that the production of two libraries (e.g., heavy and light chain) will lead to more favorable antibodies via a co-selection process, regardless of how those antibodies are produced." Present Office Action at page 19 (emphasis in original). Applicants respectfully assert that this characterization of, and reliance on, Waterhouse for such a teaching is improper because it fails to consider the reference as a whole. In particular, relying on the disclosure of Waterhouse in such a manner ignores the fact that the methods disclosed in Waterhouse are performed in a *prokaryotic* system. Waterhouse, when properly considered *as a whole--i.e.*, taking into account the fact that the immunoglobulin light and heavy chains are part of a common vector, that the fragments are fused by at least one of the chains to a phage coat protein, and that antibody fragment expression and selection are performed in prokaryotic host cells--would not be considered by one of ordinary skill in the art as reference disclosing techniques that could simply be extrapolated to a eukaryotic cell system, even in light of Zauderer, which discloses the

introduction of a single vaccinia virus expression library into eukaryotic host cells, and Rowlands, which discloses the expression of a single, previously selected antibody from a vaccinia virus expression vector in a eukaryotic cell.

As discussed above, Dr. Storkus stated in his Declaration that methods using prokaryotic expression systems could not be extrapolated to eukaryotic cells because the conditions for assembly of immunoglobulins from light and heavy chains are different in the eukaryotic cytoplasm than in the periplasmic space of a bacterial host, and that "it could not be known what effect this would have on antibody assembly." Storkus Declaration at page 4. Hence, one of ordinary skill in the art upon reading Waterhouse would not think that, because the method could be used in prokaryotes that it would also work in eukaryotes.

In view of the above, the Examiner has not provided any satisfactory reasons why one of ordinary skill in this art, seeking to select polynucleotides that encode antigen-specific immunoglobulins by introducing two expression libraries into mammalian cells, would combine Waterhouse with Rowlands and Zauderer in such a way that the present invention would be rendered obvious.

Applicants also respectfully submit that, contrary to the assertions on Page 14 of the present Office Action (and asserted again at pages 15, 17, and 18), Applicants have not attempted to overcome the rejection under 35 U.S.C. § 103 by attacking the cited references individually. Rather, Applicants have characterized what is and/or what is not disclosed by each of the cited references, and have shown why these references, either combined or individually, do not teach each and every element of the claimed invention and why there is no motivation or suggestion to one of ordinary skill in the art to combine the cited references. Namely, for the reasons discussed above, the combination

of cited references does not teach the introduction of two expression libraries encoding immunoglobulin subunit polypeptides into eukaryotic cells for selecting polynucleotides which encode an antigen-specific human immunoglobulin molecule. Even assuming, *arguendo*, that the references did teach each and every element of the claimed invention, (which they do not), Applicants respectfully maintain that, as discussed in detail above, there is no suggestion or motivation for one of ordinary skill to combine the cited references, and as discussed *infra*, no reasonable expectation of success in doing so. As such, the Examiner has not established a *prima facie* case of obviousness.

Item [3]

In alleging that Waterhouse would suggest to one of ordinary skill art to introduce two expression libraries into eukaryotic cells for selecting polynucleotides which encode an immunoglobulin molecule, the Examiner asserts that:

> A person of skill in the art (most likely a Ph.D.) working in the field of immunology and/or combinatorial chemistry (i.e., for the purpose of producing antibody and/or antibody libraries) would look to all relevant papers for guidance (e.g. papers encompassing phage display, vaccinia virus, etc.) because the problems encountered are not "unique" to any one system. The advantages obtained from producing large "primary" libraries of heavy and light chains (i.e., two libraries) and the advantages associated with being able to co-select these heavy and light chains in order to produce, for example, antibodies with high affinity are just as applicable to mammalian expression systems as they are to phage display.

Present Office Action at page 14. Applicants respectfully disagree with these assertions.

The Federal Circuit considered a similar situation in *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 U.S.P.Q. 81 (Fed. Cir. 1986), where the court held that a patent claiming a sandwich-type immunoassay that used *monoclonal* antibodies was not obvious in view of prior art references that disclosed sandwich assays using *polyclonal* antibodies, even in view of references that disclosed monoclonal

antibody production and the use of a single monoclonal antibody in a competitive immunoassay. *Id.* at 1380-81. The Federal Circuit concluded that "[f]ocusing on the obviousness of substitutions and differences instead of on the invention as a whole as the district court did in frequently describing the claimed invention as the mere substitution of monoclonal for polyclonal antibodies in a sandwich assay, was a legally improper way to simplify the difficult determination of obviousness." *Id.* at 1383.

The present case is analogous to *Hybritech* in that, here, the Examiner is focusing on the notion that a prokaryotic expression library system for selecting antibody fragments with heavy and light chain components as disclosed in Waterhouse can simply be substituted by a eukaryotic system for selecting polynucleotides encoding antigen specific immunoglobulins or fragments as in the present invention. As established in *Hybritech*, this is an improper analysis for establishing a *prima facie* case of obviousness. The present invention is not rendered obvious by a combination of references wherein one discloses that a previously selected antibody can be expressed in eukaryotic cells using vaccinia virus vectors (Rowlands), the second discloses that a single library of vaccinia virus vectors can be introduced into eukaryotic cells (Zauderer), and the third discloses a prokaryotic antibody selection system using a repertoire of heavy and light chains expressed from the same vector (Waterhouse) because the Examiner has not established that one of ordinary skill in the art would have been motivated to combine these references. In concluding otherwise, the Examiner impermissibly focuses on the obviousness of substitutions and differences instead of the invention as a whole, and uses "the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention." *See Rouffet*, 49 F.3d at 1375. Because there would have been no motivation to combine the

cited references without using the claimed invention as a guide, there is no *prima facie* case of obviousness.

Item [4]

The Examiner alleges that the Declaration of Dr. Zauderer, submitted as Exhibit B with Applicants' Reply filed July 21, 2005, is "insufficient" to overcome the rejection under 35 U.S.C. § 103 because:

> Applicants provide no factual evidence [to support the expert's opinion]. The interest of the expert in the outcome is great (i.e., it's the expert's application at issue). The opposing evidence is strong for the reasons stated in the newly amended rejection above. Finally, the nature of the matter, which Applicants are trying to establish, pertain only to legal conclusions (e.g., no motivation to combine, no reasonable expectation of success, etc.) that have been set forth in an entirely conclusory manner and thus should be afforded little or no weight. . . . In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

Present Office Action at page 15. Applicants respectfully disagree with these allegations.

Applicants respectfully submit that, contrary to the Examiner's assertion, the opposing evidence for supporting an obviousness rejection is not strong. Applicants direct the Examiner to the response set forth in Items [1] to [3], *supra*, as well Items [5] to [7], *infra*, wherein Applicants have set forth in detail why a *prima facie* case obviousness has not been properly made or supported by the Examiner. The Zauderer Declaration is consistent with and adds to the totality of the rebuttal evidence outweighing the evidence of obviousness.

Applicants also respectfully submit that the Zauderer Declaration provides more than legal conclusions that "have been set forth in an entirely conclusory manner," as alleged by the Examiner. Rather, the Zauderer Declaration provides specific reasons why, in Dr. Zauderer's opinion as an expert in the fields of immunology and cell biology, a person of ordinary skill in the art would not have been motivated to combine Rowlands with Zauderer and Waterhouse to arrive at the present invention, and would not have had a reasonable expectation of success in doing so. Specifically, Dr. Zauderer states that one of ordinary skill in this art would not have been motivated to combine Waterhouse with Rowlands and Zauderer because Waterhouse discloses a method for providing repertoires of antibody light and heavy chain fragments in the context of phage display, *i.e.*, as fusion proteins with phage surface proteins. Zauderer Declaration at pages 6-7. According to the Zauderer Declaration, one of ordinary skill in the art would not have considered the features disclosed in Waterhouse as something that could be expanded for use in eukaryotic systems (*i.e.*, prokaryotic and eukaryotic systems would not have been considered as interchangeable substitutes). *See id.* at 7. Dr. Zauderer concluded, based on the fact that the prokaryotic system of Waterhouse could not be expanded into a eukaryotic system, that one of ordinary skill in the art would not have had a reasonable expectation of success in combining Rowlands, Zauderer, and Waterhouse to arrive at the present invention. *See id.*

With respect to the Examiner's assertion that there is no showing that others of ordinary skill were working on the long-standing problem in the art that was solved by the claimed subject matter, *see* present Office Action at page 16, applicants respectfully disagree. The Examiner focuses on the fact that "the claimed invention requires expression of an antibody library using a poxvirus," and asserts that:

> The Zauderer et al. reference (WO 00/28016), which teaches the expression of protein libraries using a poxviurs, was published on May 18, 2000. There is no evidence that anyone was working on a method to express fully functional antibodies in mammalian cells using the Zauderer et al. reference. Furthermore, even if such evidence did exist, *assuming arguendo*, it would not constitute a long felt need as this paper was published fairly recently. In addition, there is no evidence that if persons skilled in the art who were presumably working on the problem knew of the teachings of the above cited reference; [sic] they would still be unable to solve the problem.

Id. Applicants respectfully submit that the Examiner is using the incorrect standard for determining a long-felt need. "Long-felt need is analyzed as of the date the problem is identified and articulated, and there is evidence of efforts to solve that problem, **not** as of the date of the most pertinent prior art references." M.P.E.P. § 716.04 (Latest Rev., Aug. 2005) (citing *Texas Instruments, Inc. v. Int'l Trade Comm'n*, 988 F.2d 1165, 1179, 26 U.S.P.Q.2d 1018, 1029 (Fed. Cir. 1993)) (emphasis added). Therefore, May 18, 2000, the publication date of Zauderer, is not the proper date for measuring the long-felt need in the art for the claimed subject matter.

The need in the art for a method of selecting polynucleotides which encode an antigen-specific human immunoglobulin molecule, or antigen-specific fragment thereof, from eukaryotic cells was well-known. Paragraphs [0003] to [0010] of the present specification and paragraphs 8, 9, 16, and 17 of the Zauderer Declaration summarize the nature of the problem in the art in isolating antigen-specific human antibodies using the alternative technologies (*i.e.*, phage display and transgenic animals) available at the time of the present invention. Evidence of the problems in the art and the long-felt need for the solution provided by the claimed invention is also found in the excerpt of the document entitled "Monoclonal Antibody Partnerships in the Biopharmaceutical

Industry," which was referenced in the Storkus Declaration and submitted as Exhibit A2 with the Reply filed July 21, 2005. Exhibit A2 presents the views of senior industry executives regarding the problems associated with the phage display and transgenic mouse technologies available prior to the present invention, as well as the type of technology in which those in the field were interested. Exhibit A2 also provides evidence that the long-felt need for the claimed invention had not been satisfied by others. *See* Exhibit A2 at page 29 (". . .We have been evaluating MAb companies for research and therapeutic uses for awhile now and we have yet to make a decision. None of the companies are a clear winner. . . "). Evidence that the long-felt need has been satisfied is presented in Exhibits B2 to B4, which accompanied the Zauderer Declaration submitted on July 21, 2005. These press releases announce collaborations between Vaccinex, Inc., exclusive licensee of the present invention, and various companies that are interested in producing antigen-specific human monoclonal antibodies for therapeutic and diagnostic purposes, and indicate that use of the claimed invention will make possible the development of antibodies that would not otherwise have been developed using the previously available technologies. In Exhibit B2, for example, the CEO, President and founder of OPi states that "Vaccinex's innovative antibody discovery technology will enable us to make a technological leap to develop new fully human antibodies aiming at treating haematological diseases." Exhibit B2 at page 1. In Exhibit B3, the CEO of Lonza Group states that: "Integrating Vaccinex's innovative library-based antibody discovery technology with the GS Gene Expression System will offer true value to customers by producing substantial quantities of high quality, fully functional human monoclonal antibodies that would have been difficult to identify with

other systems." Exhibit B3 at page 1. This evidence shows that the long-felt and unmet need in the art that is satisfied by the claimed invention.

The Examiner further contends that "Applicants' arguments are not commensurate in scope with the claimed invention. The Declaration refers only to the system described in the above-referenced application and not to the individual claims of the application." Present Office Action at page 16. Applicants respectfully disagree with these contentions. The Examiner asserts that "Applicants have already made clear that the claimed invention is not limited to an 'efficient' method for the production of 'useful' antibodies. Thus, there was not a long felt need to produce antibodies (or fragments thereof) with low binding affinity and/or specificity as these goals were readily obtainable by other means" Present Office Action at page 17. Contrary to the Examiner's assertions, Applicants arguments that there was a long-felt need for the present invention are **not** obviated by the fact that the previously available technologies sometimes worked and sometimes did not, with unpredictable reliability. The claims recite a method of selecting polynucleotides which, as part of an immunoglobulin molecule (or fragment thereof), are specific for an antigen. Immunoglobulins produced, for example, by phage display and which no longer recognize target antigen are not antigen-specific. If anything, the Examiner's focus on the unreliability of the technologies available prior to the present invention bolsters the fact that one of ordinary skill in the art at the time would not have had a reasonable expectation of success in combining the cited references to arrive at the claimed invention.

Item [5]

The Examiner disagrees with Applicants that one of ordinary skill in the art would not have reasonably expected that the phage display technology described in Waterhouse could be extrapolated to methods of introducing two random expression libraries into eukaryotic host cells. *See* present Office Action at pages 11 and 18. The Examiner asserts that, because "Rowlands et al teach a method for producing antibodies in vaccinia infected 'mammalian' cells,' that "the conclusion that a person of skill in the art would know how to express antibody in a 'mammalian' cell is reasonable." *Id.* at 18. The Examiner further asserts that because "Zauderer et al teach how to make and/or use a library of proteins using a vaccinia virus vector like the vaccinia virus vector disclosed by Rowlands. . .the conclusion that a person of skill in the art would know how to make and/or use a library of proteins, including antibodies, with a vaccinia virus is reasonable." *Id.* Applicants respectfully disagree with these assertions. As explained in detail in Items [2] and [3], *supra*, this analysis fails to consider the invention as a whole, focusing, instead, on the obviousness of differences and substitutions; it is therefore improper for establishing a *prima facie* case of obviousness.

The fact that the Examiner is focusing on the obviousness of differences and substitutions instead of the invention as a whole is evidenced on page 18 of the present Office Action, which asserts that "the prokaryotic/eukaryotic distinctions to which Applicants refer. . .are not at issue in this case." Applicants respectfully assert that, quite to the contrary, these differences are at the heart of the issue of why there would not be a motivation for one of ordinary skill in the art to combine Waterhouse with Rowlands and Zauderer, let alone a reasonable expectation of success on the part of the skilled artisan if he did combine the cited references. As set forth in Items [2] and [3], *supra*, the

Examiner's reliance on Waterhouse "to show that the production of two libraries (e.g., heavy and light chain) will lead to more favorable antibodies via a co-selection process regardless of how those antibodies are produced," present Office Action at page 19, is improper because: 1) it fails to consider the reference as a whole (*i.e.*, that it discloses the use of heavy and light chain immunoglobulin repertoires in a *prokaryotic* system); and 2) because it focuses on the obviousness of differences and substitutions in the references (*i.e.*, two expression libraries substituted for one, eukaryotic substituted for prokaryotic), rather than considering the claimed invention as a whole.

Even assuming, *arguendo*, that the Examiner could establish a motivation to combine the cited references (with which Applicants disagree), Applicants respectfully maintain that there would have been no reasonable expectation of success in doing so to achieve the claimed invention. A similar consideration was addressed by the Federal Circuit in *In re Vaeck*. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). In *Vaeck* the claimed invention was directed to a chimeric gene capable of being expressed in cyanobacteria cells, comprising a promoter region effective for expression of a DNA fragment in Cyanobacterium and at least one DNA fragment from a insecticidally active *Bacillus* bacterial gene. *Id.* The Federal Circuit determined that there was no motivation to combine, and no reasonable expectation of success in combining: 1) a reference that disclosed the expression in cyanobacteria of a chimeric gene comprising a chloroplast promoter sequence fused to a CAT selectable marker gene; and 2) three secondary references that collectively disclosed the expression of genes encoding certain *Bacillus* insecticidal genes in three different species of bacterial hosts, two of the genus *Bacillus* and *E. coli*. *Id.* The court determined that "[t]he prior art simply does not disclose or suggest the expression in cyanobacteria of a chimeric

gene encoding an insecticidally active protein, or convey to those of ordinary skill in the art a reasonable expectation of success in doing so. . . . The expression of antibiotic resistance-conferring genes in cyanobacteria, without more, does not render obvious the expression of unrelated genes in cyanobacteria for unrelated purposes." *Id.* at 493.

In *Vaeck*, the bacterial and cyanobacterial hosts that were at issue are both members of the prokaryote kingdom. *Id.* at 489. Unlike in *Vaeck*, the eukaryotic host cells in the method of the present invention and the prokaryotic host cells used in the phage display methods in Waterhouse are not even in the same taxonomic kingdom. Hence, the differences between the cited references and the claimed invention in the present case are even greater than those in *Vaeck*. *A fortiori*, the present invention is not rendered obvious by the cited references.

At the very most, the combination of Rowlands, Zauderer and Waterhouse might be an *invitation to try* selecting polynucleotides encoding an antigen-specific immunoglobulin molecule or fragment thereof in eukaryotic cells as in the present invention, "but [the cited references] do not suggest how that end might be accomplished." *See e.g., Hybritech* 802 F.2d at 1380. Furthermore, it is well established that "obvious to try" is not the standard for establishing a *prima facie* case of obviousness under 35 U.S.C. § 103. *See e.g., id.*

Accordingly, Applicants respectfully maintain that the Examiner has failed to establish a *prima facie* case of obviousness and that the rejection should be withdrawn.

Item [6]

The Examiner alleges that the Declaration of Dr. Storkus, submitted as Exhibit A with Applicants' Reply filed July 21, 2005, is "insufficient" to overcome the rejection

under 35 U.S.C. § 103 because "Applicants' arguments are not commensurate in scope with the claims." Present Office Action at page 19 (citations omitted). Applicants respectfully disagree with this allegation.

The Examiner asserts that "[t]he claims do not require 'efficient' introduction of 'good' antibodies as Dr. Storkus contends. In fact, Applicants make clear that low efficiency methods that generate poor antibodies are also to be included within the scope of Applicants' claims." *Id.* The Examiner cites Applicants' Reply filed December 7, 2004, as support for this assertion. *See id.* ("While the Specification does indicate that direct ligation results in a relatively low recombination efficiency and titer. . . it does not say that methods such as direct ligation or modified homologous recombination. . . cannot be used to generate vaccinia virus libraries. . .") (quoting Applicants Reply filed December 7, 2004, at page 22). However, the excerpts from Applicants' Reply of December 7, 2004, are inapposite to the Examiner's argument because it does not address antibody quality. Rather, these excerpts from the Applicants' Reply were made with respect to the efficiency of insertion of heterologous nucleic acid sequences into vectors in methods by which *expression libraries*, **not** antibodies, are generated.

Furthermore, the Storkus Declaration addresses the skepticism that he, as a member of Vaccinex's Scientific Advisory Board, had that the claimed invention would work "to find an antibody that had a specificity for a specific antigen of interest" when expressed from two random libraries introduced into eukaryotic host cells. *See* Storkus Declaration at page 3. As set forth in Item [4], *supra*, the claims recite a method of selecting polynucleotides which, as part of an immunoglobulin molecule (or fragment thereof), are specific for an antigen. If the immunoglobulin chains do not pair in such a way that they do not produce molecules that specifically bind an antigen, and therefore

cannot be selected, then they would not be antigen-specific. Thus, Applicants respectfully submit that the Storkus Declaration provides evidence that is commensurate with the scope of the claimed invention.

With respect to the assertions on page 20 of the present Office Action that the combined teachings of Rowlands, Zauderer and Waterhouse refute the evidence presented in the Storkus Declaration, Applicants respectfully direct the Examiner's attention to the discussion set forth in Items [1] to [5], *supra*, which details that a *prima facie* case of obviousness has not been established.

Item [7]

The Examiner asserts that "Applicants' arguments are not commensurate in scope with the claims," based on the Zauderer Declaration. *See* present Office Action at pages 12 and 21. The Examiner makes similar assertions as made with respect to the Storkus Declaration. *Compare* present Office Action at pages 19 and 21. Specifically, the Examiner asserts that "'[a]ntibodies' with 'useful' activity that recognize a specific target protein are not required. In fact, Applicants make clear that low efficiency methods that generate poor antibodies are also to be included within the scope of Applicants' claims." *Id.* at page 21. The Examiner cites to Applicants' Reply filed December 7, 2004, as supporting this assertion. *See id.* ("While the Specification does indicate that direct ligation results in a relatively low recombination efficiency and titer. . . it does not say that methods such as direct ligation or modified homologous recombination. . . cannot be used to generate vaccinia virus libraries. . .") (quoting Applicants Reply filed December 7, 2004, at page 22). As set forth in Item [6], *supra*, the excerpts from Applicants' Reply are inapposite to the Examiner's argument because they do not address antibody quality.

Rather, these excerpts from the Reply of December 7, 2004, were made with respect to efficiency of insertion of heterologous nucleic acid sequences into vectors in methods by which *expression libraries*, **not** antibodies, are generated.

Furthermore, with respect to generating "useful antibodies," as set forth in Items [4] and [6], *supra*, the claims recite a method of selecting polynucleotides which, as part of an immunoglobulin molecule (or fragment thereof), are specific for an antigen. If the immunoglobulin chains do not pair in such a way that they do not produce molecules that specifically bind an antigen, and therefore cannot be selected, then they would not be antigen-specific.

In addressing Exhibits B2 to B4 that were submitted with Applicants Reply filed July 21, 2005, the Examiner has focused on the specific uses to which each of the three companies partnering with Vaccinex in Exhibits B2 to B4 will put the claimed invention. However, Exhibits B2 to B4, collectively, are *representative* of how a long-felt need in the art was met by Applicants' invention. While each of these business organizations has, at a certain level of specificity, its own uses for the claimed invention (*e.g.*, developing antibodies to its own antigenic targets of interest), the diversity of uses for the claimed invention *among* various companies, as represented by Exhibits B2-B4, is evidence that the claimed invention has broader applicability than any of the single uses of any one company. Hence, it is not necessary that the claimed invention recite limitations that reflect, for example, all of the specific antigenic targets in which anyone who licenses the claimed invention may be interested in order for these Exhibits to have probative value as objective evidence of nonobviousness. Rather, it is sufficient that numerous business organizations are interested in using the claimed technology to fill a need that was not met by the prior art methods.

Finally, the Examiner asserts that "Applicants have not established a nexus between the claimed invention and the licenses." Present Office Action at pages 23-24. Applicants respectfully submit that the Examiner appears to be conflating the idea of showing the existence of licenses by competitors in a market to establish commercial acquiescence, as a secondary indicator of non-obviousness, with the use for which Applicants submitted Exhibits B2 to B4, which is to show that various business organizations are interested in entering strategic alliances to use the claimed invention because the prior art technologies were unsuitable for their needs. As such, Applicants believe that the Examiner's arguments on pages 23 to 24 are moot.

Summary

For the reasons set forth in Items [1] to [7], supra, Applicants respectfully submit that the rejection of claims 84, 88-97, 99, 103, 107-122, and 127-131 (as presented in Applicants Reply filed July 21, 2005) under 35 U.S.C. § 103(a) as allegedly being unpatentable over Rowlands, Zauderer, and Waterhouse has been overcome or otherwise rendered moot because: 1) the cited references fail to each all of the elements of the claimed invention; 2) one of ordinary skill in the art would not have been motivated to combine the cited references; and 3) the cited references would not have conveyed to one of ordinary skill in a reasonable expectation of success in achieving the claimed invention. Furthermore, the claimed invention meets a long-felt need in art for an antibody selection technology alternative to phage display and transgenic animals.

The Rejection of Claims 84, 88-97, 99, 103, 107-122, and 127-131 as Presented Herein, is Traversed.

For the reasons described in detail above, Applicants traverse the rejection of claims 84, 88-97, 99, 103, 107-122, and 127-131 under 35 U.S.C. § 103 and believe that the rejection was improper. Nevertheless, solely in an effort to facilitate prosecution of the claims in the captioned application, and not in acquiescence to any of the Examiner's rejections, Applicants have amended claims 34, 86, 87, 89, 90, 91, 93-97, 107, 128, 129, and 131 to delete the phrases "or antigen specific fragment thereof" and "or fragment thereof."

Given that the combination of cited references does not render obvious the claims as presented in Applicants' Reply filed July 21, 2005, for the reasons set forth in detail, *supra*, the cited references do not render obvious the claims as amended herein. As set forth *supra*, Applicants reserve the right to pursue the claims in the form presented in the Reply filed July 21, 2005, in one or more continuing applications.

In particular, the claims as amended are directed to full immunoglobulin molecules. Rowlands, Zauderer, and Waterhouse do not teach or suggest a method of selecting polynucleotides which encode antigen-specific full immunoglobulin molecules from two expression libraries as in the presently amended claims. Rowlands describes the expression of a previously selected antibody from vaccinia virus vectors in a eukaryotic cell. Zauderer describes the introduction of a single expression library into eukaryotic cells. Waterhouse describes only the generation of antibody fragments fused to phage coat proteins for phage display in a prokaryotic host. Therefore, the cited references do not teach each and every element of the claimed invention. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejection Based on Non-Statutory Obviousness-Type Double Patenting

In the Office Action at pages 24-25, the Examiner has provisionally rejected claims 84, 88-97, 99, 103, 107-122, and 127-131, for alleged obviousness-type double patenting over claims 1-84 of commonly-owned U.S. Patent Application Publication No. 2003/0104402 A1 ("the '402 publication") in view of Rowlands. Applicants respectfully traverse this rejection, and contend that claims 84, 88-97, 99, 103, 107-122, and 127-131 would not have been obvious to one of ordinary skill in the art over claims 1-84 of the '402 Publication in view of Rowlands.

One of ordinary skill in the art would not have had a reasonable expectation of success in combining Rowlands with the '402 publication to arrive at the present invention. Rowlands describes the use of vaccinia virus vectors for making an *individual* recombinant antibody, not an immunoglobulin expression library. There would have been no indication to one of ordinary skill in the art that the methods for making or screening a library of intracellularly expressed immunoglobulins, as described in the '402 publication could be used to make or screen a library of extracellularly expressed immunoglobulins as in the present invention based on the disclosure in Rowlands of an *individual antibody* that is expressed extracellularly. The Examiner is improperly focusing on the obviousness of differences and substitutions in making this rejection rather than on the invention as a whole. *See Hybritech*, 802 F.2d at 1383. Selection of previously unknown polynucleotides from the intracellular expression of two libraries of immunoglobulin heavy and light chains as disclosed in the '402 application is different than the expression of a single, previously selected antibody that is secreted into the culture medium as in Rowlands. Applicants respectfully submit that, as with respect to

making a *prima facie* case of obviousness under 35 U.S.C. Section 103, it is improper "to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.'" *In re Hedges*, 783 F.2d 1038, 1041, 228 U.S.P.Q. 685 (Fed. Cir. 1986) (quoting *In re Wesslau*, 353 F.2d 238, 241 147, U.S.P.Q. 391, 393 (CCPA 1965)). Reconsideration and withdrawal of the rejection therefore are respectfully requested.

However, if the Examiner is not inclined to withdraw the rejection, then Applicants respectfully request that it be held in abeyance until such time as otherwise patentable subject matter has been identified in either the present application or the '402 publication. At that time, Applicants will consider filing a terminal disclaimer to obviate the double-patenting rejection.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Tracy L. Muller
Attorney for Applicants
Registration No. 55,472

Date: February 2, 2006

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600
488112_1.DOC